Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 5, and 25-27 are under consideration in the application, with claims 1 and 27 being the independent claims. Claims 4 and 18 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 25-27 are sought to be added. Support for the amendments and the new claims can be found throughout the specification and in the claims as originally filed. In particular, support for the changes can be found, *inter alia*, in the specification on page 9, fourth paragraph; on page 10, last paragraph; on page 14, last paragraph; on page 20, last paragraph; and in the Examples, particularly Examples 1 and 2, beginning on page 24. In addition, the specification has been amended to include sequence identifiers. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Election / Restriction

The Examiner acknowledged Applicants' election without traverse of Group I. (*See* Paper No. 14, page 2.) In addition, the Examiner withdrew claims 6-17, 19-21, 23 and 24 from further consideration as being drawn to a non-elected invention and made the restriction the requirement final. (*See id.*)

Objection to the Specification

The Examiner objected to the specification for lacking sequence identifiers, specifically on pages 24-27 and Figures 1-4. (*See* Paper No. 14, page 2.) Applicants have amended the specification to insert sequence identifiers in accordance with 37 C.F.R. § 1.821(d). Accordingly, Applications respectfully request that the objection be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-5 and 18 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO 91/08291 (Levinson *et al.*). (*See* Paper No. 14, page 2.) Applicants respectfully traverse this rejection as it may apply to the amended claims.

For a reference to be anticipatory under 35 U.S.C. § 102(b), the reference must teach each and every element of the claimed invention. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); *see also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) ("The identical invention must be shown in as complete detail as is contained in the . . . claim."). Applicants assert that WO 91/08291 does not fulfill this requirement.

WO 91/08291 discusses the combination of TGF-β LAP with mature TGF-β to form a latent TGF-β. The reference does not disclose, however, a method for providing latency to a cytokine comprising covalently linking a fusion protein comprising a latency associated peptide and a proteolytic cleavage site with a cytokine, wherein the fusion protein is heterologous to the cytokine and wherein the fusion protein is covalently linked to the cytokine. For example, the reference does not teach the addition of a proteolytic cleavage site with the LAP. In addition, this reference neither teaches a LAP-proteolytic cleavage site

fusion protein heterologous to the covalently linked cytokine, nor, as noted by the Examiner, the "association of latency associated peptide with other factors." (Paper No. 14, page 3.)

Since WO 91/08291 fails to teach each and every element of the claimed invention, the reference does not anticipate the invention of claims 1-3, 5 and 25-27. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-5 and 18 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 91/08291 in view of U.S. Patent No. 5,908,626 (the '626 patent). (*See* Paper No. 14, page 3.) In particular, it was the Examiner's position that

> [i]t would have been obvious to one of ordinary skill in the art, on reading the teachings of WO 91/08291 and the '626 patent, to substitute a cleavable latency associated peptide for the Fc protein of the '626 patent, thus generating a fusion protein comprising latency associated peptide, a cleavage site, and cytokine. One of ordinary skill would have been motivated to do so because WO 91/08921 teaches that a cleavable complex of latency associated peptide and the cytokine TGF-β is useful for the administration of TGF-β, and the '626 patent teaches that stabilization of other cytokines is desirable and can be achieved by fusion with the appropriate molecule.

(Paper No. 14, pages 3-4.) Applicants respectfully traverse this rejection as it may apply to the amended claims.

To support a *prima facie* case of obviousness, there must be a motivation to combine the art references, there must be a reasonable expectation of success, and the art references must teach all of the claim limitations. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). WO 91/08291, as discussed *supra*, does not teach the claimed invention.

The '626 patent does not remedy this deficiency, as it discusses merely the fusion of an immunoglobulin Fc fragment to an interferon-beta or the conjugation of interferon-beta with gelatin to purportedly increase the half life of the interferon. However, the '626 patent does not provide any data to support the proposition that the IFNβ:Fc hybrid would be "expected to have a longer half-life in vivo than native IFNβ." The '626 patent, col. 4, lines 19-20. Also, the Fc fragment and gelatin do not confer latency to the interferon. In addition, the '626 patent does not teach the use of any other peptide to be substituted in the fusion protein for the Fc fragment. As such, Applicants assert that the references do not teach all of the claimed limitations either singularly or in combination.

Since at least one of the requirements for establishing a *prima facie* case of obviousness has not been met, the present invention is nonobvious over the cited references. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-5 and 18 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification. Specifically, the Examiner asserted that

> while being ***enabling*** for fusion of a latency associated peptide with cytokines, does not reasonably provide enablement for fusion of such peptides with all pharmaceutically active agents, nor for the treatment of all diseases with all such agents. The specification does not enable any person skilled in the art to which it pertains . . . to make and use the invention commensurate in scope with these claims.

(Paper No. 14, page 4.)(Emphasis added.) Applicants respectfully traverse this rejection as it may apply to the amended claims.

Without acquiescing to the Examiner's rejections and solely in an effort to advance prosecution, Applicants have amended claim 1, from which claims 2, 3, 5, 25 and 26 depend, to recite a method for providing latency to a cytokine by covalently linking a fusion protein and a proteolytic cleavage site with a cytokine. As noted by the Examiner, the specification enables such a method. As such, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement be withdrawn.

With respect to claim 18, the Examiner asserted that

> [i]t encompasses all diseases, including those for which no treatment is known in the art. What is shown is the treatment of inflammatory disease by interferons. One of skill in the art would not predict, based on Applicant's disclosure of one condition, that all diseases, including diseases unrelated to inflammation and diseases not known to be treatable, could be treated by the claimed method.

(Paper No. 14, page 5.)

Applicants note that claim 18 has been cancelled and that new independent claim 27 is now drawn to a method of treating inflammatory disease. Guidance for using the method for treating inflammatory disease can be found, *inter alia*, in Example 5. Applicants submit that the specification clearly enables one of skill in the art to make and use the invention commensurate in scope with the amended claims. Therefore, Applicants respectfully request that the rejection of claim 18, as it may apply to new claim 27, be withdrawn.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-5 and 18 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. (*See* Paper No. 14, page 6.) Specifically, the Examiner alleged that "associating" a fusion protein with an agent is not defined by the specification and that one of skill in the art would be unable to determine how the agent is associated with the fusion protein. (*See id.)* Applicants respectfully traverse this rejection as it may apply to the amended claims.

Without acquiescing to the Examiner's rejections and solely to advance prosecution, Applicants have amended the pending claims such that the fusion protein is covalently linked to a cytokine. A covalent bond or "link" is well known in the art as a specific type of chemical bond. One example of covalent link is the peptide bond, as described in the specification on page 18, fourth full paragraph, and in the Examples. Applicants assert that one skilled in the art would clearly be able to determine the metes and bounds of the presently claimed subject matter. Consequently, Applicants request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Objections to the Claims

The Examiner objected to claim 18 "as depending from a non-elected claim." (Paper No. 14, page 6.) Applicants have canceled claim 18, thereby rendering this objection moot. Accordingly, Applicants request that the objection be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Specification:

The paragraph beginning on page 21, line 28, was substituted with the following paragraph:

FIGURE 1 shows nucleotide (SEQ ID NO:19) (A) and corresponding amino acid (SEQ ID NO:20) (B) sequence of the LAP-mIFNβ construct. The boxed sequence corresponds to the sequence of the MMP cleavage site including linker sequence;

The paragraph beginning on page 22, line 1, was substituted with the following paragraph:

FIGURE 2 shows nucleotide (SEQ ID NO:21) (A) and corresponding amino acid (SEQ ID NO:22) (B) sequence of the mIFNβ-LAP construct. The boxed sequence corresponds to the sequence of the MMP cleavage site including linker sequence;

The paragraph beginning on page 22, line 5, was substituted with the following paragraph:

FIGURE 3 shows amino acid sequences of the precursor domain of TGFβ 1 (SEQ ID NO:23), 2 (SEQ ID NO:24) and 3 (SEQ ID NO:25) (human, Hu), TGFβ 4 (SEQ ID NO:26) (chicken, Ck), TGFβ 5 (SEQ ID NO:27) (frog, Fg). Arrows indicate the position of the proteolytic processing resulting in cleavage of the signal peptide of TGFβ 1 and of the mature TGFβs. N-linked glycosylation sites are underlined, as is the integrin cellular recognition sequence (Roberts and Sporn, Peptide Growth Factors and their Receptors: Sporn, MB and Roberts, AB, Springer-Verlag, Chapter 8, 422 (1996));

The paragraph beginning on page 22, line 14, was substituted with the following paragraph:

FIGURE 4 shows the sequences (SEQ ID NOs:28-100) of protein cleavage sites of matrix metalloproteinases (MMPs) (Nagase and Fields, Biopolymers, 40, 399-416 (1996));

The paragraph beginning on page 24, line 17, was substituted with the following paragraph:

Double stranded deoxyoligonucleotide coding for the sequence GLY GLY GLY GLY SER PRO LEU GLY LEU TRP ALA GLY GLY GLY SER (SEQ ID NO:1) was designed as follows:

Sense oligo:

5'AATTCGGGGGAGGCGGATCCCCGCTCGGGCTTTGGGCGGGAGGGGGC TCAGC 3' (SEQ ID NO:2)

Antisense oligo:
5' GGCCGCTGAGCCCCCTCCCGCCCAAAGCCCGAGCGGGGATCCGCCTCC CCCG 3' (SEQ ID NO:3)

The paragraph beginning on page 25, line 11, was substituted with the following paragraph:
Sense Primer 5' CCAAGCTTATGCCGCCCTCCGGGCTGCGG 3' (SEQ ID NO:4)
Antisense primer 5' CCGAATTCGCTTTGCAGATGCTGGGCCCT 3' (SEQ ID NO:5)

The paragraph beginning on page 25, line 20, was substituted with the following paragraph:
Sense primer 5' CGCGGCCGCAATCAACTATAAGCAGCTCCAG 3' (SEQ ID NO:6)
Antisense primer 5' GGTCTAGATCAGTTTTGGAAGTTTCTGGTAAG 3' (SEQ ID NO:7)

The paragraph beginning on page 26, line 3, was substituted with the following paragraph:
Sense primer 5' CCAAGCTTATGAACAACAGGTGGATCCTC 3' (SEQ ID NO:8)
Antisense primer 5' CCGAATTCGTTTTGGAAGTTTCTGGTAAG 3' (SEQ ID NO:9)

The paragraph beginning on page 26, line 11, was substituted with the following paragraph:
Sense primer 5' CGCGGCCGCACTATCCACCTGCAAGACTATC 3' (SEQ ID NO:10)
Antisense primer 5' GGTCTAGATCAGCTTTGCAGATGCTGGGCCCT 3' (SEQ ID NO:11)

The paragraph beginning on page 26, line 24, was substituted with the following paragraph:
Sense primer starting at signal peptide was 5' CGCCCATGGCGCCTTCGGGGCCT 3' (SEQ ID NO:12). This primer has a modified sequence around the initiator ATG to create a Nco1 site.
Antisense primer 5' CCGAATTCGCTGTGCAGGTGCTGGGCCCT 3' (SEQ ID NO:13)

The paragraph beginning on page 27, line 7, was substituted with the following paragraph:
To avoid processing of the LAP-mIFNβ protein at Arg 278 of LAP, LAP spanning amino acids Met 1-Ser 273 was cloned. This sequence was followed by a flexible linker (GGGGS, SEQ ID NO:14), a putative MMP9 (Peng et al., Human Gene Therapy, 8, 729-738 (1997); Ye et al., Biochemistry, 34, 4702-4708 (1995)) or putative MMP1 (Nagase and Fields, Biopolymers, 40, 399-416 (1996)) cleavage site (PLGLWA, SEQ ID NO:15) and another flexible portion (GGGGSAAA, SEQ ID NO:16) followed by mature mIFNβ (starting at amino acid Ile-22). Embedding the MMP cleavage site in a hydrophilic area should facilitate access to enzymatic attack. The core of the cleavage site (PLGL, SEQ ID NO:17) has been shown to be cleaved as a peptide by MMP2 and in a different version (PLGI, SEQ ID NO:18) also by MMP3, MMP7 and MMP8 (Nagase and Fields, Biopolymers, 40, 399-416 (1996)) .

The paragraph beginning on page 27, line 22, was substituted with the following paragraph:

The unprocessed LAP-mIFNβ (SEQ ID NO:20) and mIFNβ-LAP (SEQ ID NO:22) fusion proteins have an expected molecular weight of 52,375 and 51,768 Daltons respectively. The primary sequence of these fusion proteins contains four possible N-glycosylation sites. A schematic representation of the primary structure and putative folding of these proteins and their possible interaction with LTBP is shown in Fig. 5. On the right panel of Figure 5B the folding of LAP-mIFNβ is shown resembling the folding of native TGFβ. Near the amino terminal end (N) of the LAP-mIFNβ, Cys 33 interacts with the third 8-cysteine-rich repeat of LTBP, whilst Cys 224 and 226 are expected to dimerize the protein by intermolecular disulphide bonds (Saharinen et al., Cytokine and Growth Factors, 10, 99-117 (1999)). On the left panel of Figure 5B, the structure of mIFNβ-LAP is shown. Cys 33 is now located behind the MMP cleavage site and Cys 224 and 226 are closer to the carboxy (C) end of the protein.

In the Claims:

Claims 4 and 18 were cancelled.

Pending claims 1 and 5 were substituted with the following claims 1 and 5:

1. (Twice amended) A method for providing latency to a [pharmaceutically active agent] cytokine comprising [associating] covalently linking a fusion protein comprising a latency associated peptide and a proteolytic cleavage site with a [pharmaceutically active agent] cytokine, wherein said fusion protein is heterologous to said cytokine and wherein said fusion protein provides latency to said [pharmaceutically active agent] cytokine.

5. (Twice amended) The method of claim 1 wherein the fusion protein is [in association with] covalently linked to the latent TGFβ binding protein (LTBP).

Claims 25-27 were added.